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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/048,013	04/29/2002	Michael Luconi	LUCONI1	1351

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BROWDY AND NEIMARK, P.L.L.C.
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EXAMINER

WOOD, AMANDA P

ART UNIT	PAPER NUMBER
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1657

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/12/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.		Applicant(s)	
	10/048,013		LUCONI ET AL.	
	Examiner		Art Unit	
	Amanda P. Wood		1657	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 25 January 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1, 4, 5, 7-9, 12, 19, 20, 26 and 27 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1, 4, 5, 7-9, 12, 19, 20, 26, and 27 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION
Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 25 January 2007 has been entered.

Claims 1, 4, 5, 7-9, 12, 19, 20, 26, and 27 have been examined on the merits.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 4, 5, 7-9, 12, 19, 20, 26, and 27 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Claim 1 contains the phrase "treating human seminal liquid comprising spermatozoa...for up to two hours...thereby increasing spermatozoa motility during the up to two hours of treatment." While Applicant is enabled for treating seminal liquid comprising spermatozoa for two hours, Applicant is not enabled for treating seminal liquid for less than two hours, and has not shown that treating said seminal liquid for less than two hours would

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increase spermatozoa motility during that less than two hours of treatment time. Applicant has only shown evidence that treating the seminal liquid for two hours will increase spermatozoa motility at or beyond the two hour time-point, not during the two-hour time period of treatment, as argued. Furthermore, the state of the art (i.e., Nass-Arden et al) shows that treatment of spermatozoa with PI3K inhibitor during the first two hours actually inhibits motility, whereas motility is increased in the spermatozoa after the two hours of treatment. It would take an undue amount of experimentation for one of ordinary skill in the art to practice the invention, as claimed, due to the current state of the art and the lack of enablement provided in the instant specification for treating the seminal liquid for less than two hours with PI3K inhibitor.

All other claims depend directly or indirectly from rejected claims and are, therefore, also rejected under USC 112, first paragraph for the reasons set forth above.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 1 recites the limitation "separating the spermatozoa by spermatozoa separation methods used in assisted reproduction techniques (ART)" in lines 10-11. There is insufficient antecedent basis for this limitation in the claim (i.e., this method limitation does not relate to the preamble of the instant claim.)

All other claims depend directly or indirectly from rejected claims and are, therefore, also rejected under USC 112, second paragraph for the reasons set forth above.

Claim Rejections - 35 USC § 103

Claims 1, 4, 5, 7-9, 12, 19, 20, 26, and 27 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Nass-Arden et al (Mol. Reprod. Dev. 1990) in view of Vlahos et al (J. of

Biol. Chem. 1994) and Bonjouklian et al (US 5,378,725) for the reasons set forth in the previous office action which are restated below.

Nass-Arden et al teach a method wherein mammalian sperm (i.e., seminal liquid comprising spermatozoa) is treated with quercetin (i.e., an inhibitor of phosphatidylinositol 3-kinase) so as to increase the motility of the sperm. Nass-Arden et al further teach a method wherein the sperm are separated by sperm separation methods used in ART (i.e., assisted reproduction techniques), such as the wash and spin method, the sedimentation method, or the pellet and swim-up method. Furthermore, Nass-Arden et al teach that in the first two hours of treatment with quercetin, motility is inhibited in sperm, but afterward, motility intensity and duration is enhanced. In addition, Nass-Arden et al teach that untreated sperm show no motility after 3.5 hours, whereas the sperm treated with the phosphatidylinositol 3-kinase inhibitor quercetin show high motility at this point, and continue to show high motility for an additional 2-3 hours. Furthermore, Nass-Arden et al teach that quercetin might be a good candidate to increase the fertilizing potential of spermatozoa (see, for example, Abstract, pg. 369, col. 2, pg. 370, col. 1, col. 2, and pg. 373, col. 1).

Vlahos et al beneficially teach that quercetin is a known inhibitor of phosphatidylinositol 3-kinase that is directed at the ATP-binding site of the kinase. Vlahos et al also beneficially teach that quercetin has also been shown to inhibit other phosphatidylinositols and protein kinases, which can be an unwanted side effect of using this particular inhibitor. For this reason, Vlahos et al teach that it would be beneficial to find other inhibitors of phosphatidylinositol 3-kinase that do not affect phosphatidylinositol 4-kinase or other selected protein kinases. Vlahos et al beneficially teach that 2-(4-morpholinyl)-8-phenyl-4H-1-benzopyran-4-one, or (LY294002), completely and specifically abolished phosphatidylinositol 3-kinase activity but did not inhibit any other tested protein or lipid kinases. Vlahos et al beneficially teach that LY294002 was

efficacious in inhibiting phosphatidylinositol 3-kinase activity in whole cell assays (e.g., human neutrophils and sperm) as well as in purified phosphatidylinositol 3-kinase (see, for example, Abstract, pg. 5247, col. 2).

Bonjouklian et al beneficially teach that wortmannin and its analogs can be used in humans to inhibit phosphatidylinositol 3-kinase in lysed or whole cells.

It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the method disclosed by Nass-Arden et al based upon the beneficial teachings provided by Vlahos et al, with respect to the art-recognized method of substituting one inhibitor for a more specific inhibitor, and by Bonjouklian et al, with respect to the fact that inhibitors of phosphatidylinositol 3-kinase for use in humans are well known in the art, as discussed above. Furthermore, Nass-Arden et al beneficially teach that quercetin-treated sperm have greater motility for longer duration than untreated sperm, and that treatment with such a compound may increase the fertilizing potential of spermatozoa, and therefore, it would have been both obvious and beneficial for the skilled artisan to use the methods taught by Nass-Arden et al to treat human sperm so as to increase their motility for use in ART procedures. Bonjouklian et al teach that wortmannin and its analogs can be used in humans to inhibit phosphatidylinositol 3-kinase from both lysed and whole cells. Furthermore, Vlahos et al particularly teach that quercetin is a known inhibitor of phosphatidylinositol 3-kinase, and that it also inhibits other enzymes, which is an undesirable side effect. Vlahos et al further point out that it would be beneficial to find inhibitors of phosphatidylinositol 3-kinase that do not affect any other enzymes, and therefore, Vlahos et al teach that LY294002 is a specific inhibitor of phosphatidylinositol 3-kinase that is effective in whole-cell assays using human neutrophils. Based upon the beneficial teachings of Nass-Arden et al, Bonjouklian et al, and Vlahos et al, it would have been obvious to one of ordinary skill in the art to treat human seminal fluid

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comprising spermatozoa with a phosphatidylinositol 3-kinase inhibitor such as LY294002, wortmannin, or quercetin, or derivatives thereof and to use a method well-known in ART to separate the spermatozoa. In addition, based upon the known properties of these phosphatidylinositol 3-kinase inhibitors (i.e., the delayed onset of increased sperm motility), it would have been obvious to one of ordinary skill in the art to provide a medium for storage and/or transportation of mammalian spermatozoa comprising such an inhibitor, so as to provide a means for maximizing the sperm's motility upon arrival at the treatment clinic and/or upon the laboratory's need for the sperm in the ART procedure (i.e., IVF, GIFT, and IUI). Furthermore, based upon the knowledge that treatment of sperm with a PI3K inhibitor increases the motility of normal sperm, one of ordinary skill in the art would have had a reasonable expectation of success of increasing the motility of abnormal sperm for the expected benefit of increasing the fertilization potential of said sperm, whether for use in ART procedures or for animal husbandry. The result-effective adjustment of particular conventional working conditions (e.g., using a particular amount of a particular phosphatidylinositol 3-kinase inhibitor, treating seminal liquid for a particular amount of time, and/or using a particular method of separation or ART therapy) is deemed merely a matter of judicious selection and routine optimization which is well within the purview of the skilled artisan.

Response to Arguments

Applicant's arguments filed 19 December 2006 have been fully considered but they are not persuasive. Applicant argues that Nass-Arden et al teach away from the present invention. The Examiner respectfully disagrees. The Examiner would like to point out that Nass-Arden et al teach in Figure 1 (page 371) that at 2 hours of treatment, the motility of sperm treated with PI3K inhibitor is significantly increased compared to that of controls (i.e, percent motility is

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increased by about the same amount as that taught by Applicant). Therefore, Nass-Arden et al teach that at the two-hour time point, motility was increased in treated sperm, and therefore Nass-Arden et al teach a method wherein sperm are treated with PI3K inhibitor for 2 hours, whereby sperm motility is increased at the 2 hour point. In addition, Applicant argues that Nass-Arden et al do not teach a method using human sperm from an oligospermic, asthenospermic, teratospermic, or oligoasthenospermic patient. Based upon the teachings of Nass-Arden et al, and the level of skill of one in the art, it would have been obvious for one of skill and knowledge in the art to use the methods provided by Nass-Arden et al to treat patients having said sperm pathologies for the expected benefit of increasing the motility of abnormal or immotile sperm to increase the fertilization potential of said sperm in ART procedures. Furthermore, one of ordinary skill in the art would have expected such methods as those provided by Nass-Arden et al, which work on normal sperm of mammals used in animal husbandry techniques, to be useful on both normal and abnormal sperm of humans in ART. Furthermore, Applicant has argued that the effect of PI3K inhibitor on human sperm from oligospermic, asthenospermic, teratospermic, or oligoasthenospermic patients is surprisingly and unexpectedly more pronounced the more serious the sperm pathology of the patient, and that this unexpected result renders the instant claims non-obvious in view of the cited references. However, Applicant cites no data or evidence to support these claims of unexpected results, other than the same claims, recited in the instant specification on page 13. Therefore, the Examiner has considered Applicant's opinion regarding the unexpected results, but does not find it persuading. Therefore, based upon the teachings of Nass-Arden et al in view of Vlahos et al and Bonjouklian et al, it would have been obvious to provide the instantly claimed method for increasing spermatozoa motility.

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Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amanda P. Wood whose telephone number is (571) 272-8141. The examiner can normally be reached on M-F 8:30AM -5PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber can be reached on (571) 272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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Examiner
Art Unit 1657

APW


CHRISTOPHER R. TATE
PRIMARY EXAMINER